Complete Summary

GUIDELINE TITLE

Subclinical thyroid disease: scientific review and guidelines for diagnosis and management.

BIBLIOGRAPHIC SOURCE(S)

Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004 Jan 14;291(2):228-38. [96 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Subclinical (mild) thyroid disease (subclinical hypothyroidism and subclinical hyperthyroidism)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Screening
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To define subclinical thyroid disease, review its epidemiology, recommend an appropriate evaluation, explore the risks and benefits of treatment and consequences of nontreatment, and determine whether population-based screening is warranted

TARGET POPULATION

- Individuals with subclinical hyperthyroidism or subclinical hypothyroidism (evaluation and treatment)
- Pregnant women or women who wish to become pregnant who have subclinical hypothyroidism (evaluation and treatment)
- Individuals at high risk for thyroid dysfunction, including women older than 60 years, those with a family history of thyroid dysfunction, individuals with type I diabetes mellitus, and individuals with autoimmune disorders or atrial fibrillation (screening)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation/Screening

1. Serum thyroid stimulating hormone (TSH) levels
2. Serum free thyroxine (FT_4) concentration
3. Serum total triiodothyronine (T_3) or free T_3 concentration
4. Anti-thyroid peroxidase (TPO) antibody levels (not recommended routinely)
5. Evaluation for signs and symptoms of thyroid disease, previous treatment for thyroid disease, or family history of thyroid disease
6. Evaluation for atrial fibrillation or other cardiac disease
7. Lipid profiles
8. Population-based screening for thyroid disease (not routinely recommended; case ascertainment in high-risk groups is encouraged)

Treatment

1. Levothyroxine therapy
2. Thyroid hormone therapy
3. Antithyroid drug therapy
4. Use of beta-blockers
5. Radioiodine therapy
6. Partial thyroidectomy

MAJOR OUTCOMES CONSIDERED

- Prevalence of subclinical hypothyroidism and hyperthyroidism in the US adult population
- Morbidity and mortality related to thyroid dysfunction
- Symptomatic benefit of therapy for hypothyroidism or hyperthyroidism
- Progression to overt symptomatic hyperthyroidism or hypothyroidism
- Cardiac dysfunction or adverse cardiac end points
- Adverse outcomes of pregnancy for either the fetus or the mother
- Changes in bone mineral density (BMD)
- Risk of fractures
- Systemic hyperthyroid and neuropsychiatric symptoms
- Total and low-density lipoprotein (LDL) cholesterol levels

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Lewin Group, an independent consulting organization, was contracted to review the literature and summarize the evidence relating to the clinical questions. Relevant articles were identified by searching MEDLINE, EMBASE, Biosis, the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, and several National Health Services (UK) databases, including the Database of Abstracts of Reviews of Effectiveness, the Economic Evaluation Database, and the database of the International Network of Agencies for Health Technology Assessment. Key search terms were subclinical (text word) or subclinic* and hypothyroidism or thyroid deficien* or thyroid insufficien*; subclinical (text word) or subclinic* and hyperthyroidism or thyrotoxicosis or overactive thyroid. The following areas were evaluated (key words in parentheses): epidemiology (etiology or ethnology or epidemiology or mortality), screening (screening or thyroid function tests), treatment (therapy or treatment or radiotherapy or surgery or complication or hormon*), consequences of no treatment (complications or mortality), and economics (cost or costs or cost analysis or cost-benefit or cost effective*).

All English-language research articles or translations published on the topic from 1995 to July 2002 were reviewed, as well as 21 relevant articles and 4 abstracts published before 1995 that were identified by the planning committee. Excluded were editorials, individual case studies, studies enrolling fewer than 10 patients, and many nonsystematic reviews. The final count was 195 articles, including the earlier relevant publications identified by the planning committee.

NUMBER OF SOURCE DOCUMENTS

195

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Strength of the Overall Evidence

Good
Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair
Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.

Insufficient
Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Source: Adapted from the US Preventive Services Task Force, Agency for Healthcare Research and Quality.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The evidence report consisted of tables and summaries of each subject area indicating the authors, year of publication, numbers of subjects, nature of study (e.g., cohort, blinded, randomized), and principal findings. The complete report is available at http://www.endo-society.org/educationevents/print/evidence-report.cfm.

On the first 1 1/2 days of the consensus conference, 12 experts identified by the planning committee presented reviews of selected areas including epidemiology, laboratory testing, symptoms, effects on bone, lipids, and cardiovascular systems, screening, and effects of treatment to the panel and audience. These expert presenters left the conference at the end of the information gathering session. Over the remaining 1 days, the panel discussed the information presented and the data abstracted from the literature review to address the questions posed by the planning committee.

The expert panel assessed the data for quality, scope, and relevance. Using criteria adopted from the US Preventive Services Task Force (USPSTF), the panel rated the strength of the available evidence as either good, fair, or insufficient as it related to the association of thyroid status or benefits of treatment to specified outcome.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Representatives of the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists (AACE), and the Endocrine Society formed a planning committee for a consensus development conference to review the literature and attempt to formulate some recommendations to guide clinical practice. The committee adopted an approach patterned on the National Institutes of Health (NIH) consensus development process. The planning committee drafted a series of clinically relevant questions related to the diagnosis and management of subclinical hypothyroidism and hyperthyroidism. These questions were

- What is the definition of subclinical thyroid disease?
- What is the epidemiology of subclinical thyroid disease?
- What are the consequences of untreated subclinical thyroid disease? How should it be evaluated?
- What are the risks and benefits of treatment for subclinical thyroid disease?
- Is screening for subclinical thyroid disease warranted?

The questions were presented to a panel of 13 experts selected by the planning committee who were either senior endocrinologists not known to publish or be advocates in this area or experts in other relevant fields. Members of the planning committee were not members of the panel. Eight of the panelists were experts in thyroid disease and the remaining 5 had expertise in cardiology, epidemiology, biostatistics, evidence-based medicine, health services research, general internal medicine, and clinical nutrition.

The conference was held September 21-23, 2002. The meeting was open to the public and attended by members of the 3 sponsoring societies (i.e., the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society).

Given the paucity of randomized controlled trials (RCTs), the panel relied on the available published evidence as well as that presented during the expert presentations, particularly for data related to clinical outcomes. When evidence was not available, was contradictory, or was judged to be insufficient, the panelists relied on their experience, judgment, and interpretation of the available literature in formulating recommendations for clinical practice. Differences of opinion were settled by a majority vote after extensive discussion. The recommendations for clinical practice were developed on the basis of the evidence evaluations during the conference deliberations.

Each clinical practice recommendation was rated by individual members of the panel for strength of supporting evidence (good, fair, insufficient, or based on expert opinion). Panel members were asked to indicate their level of agreement (none, minimal, moderate, or strong) with each recommendation. Panel members submitted their assessments of the strength of evidence and their support for the recommendations during their review of the draft manuscript. A summary of the panelist's assessment of the strength of evidence and his/her degree of support for each recommendation is available at http://www.endo-society.org/educationevents/print/evidence-report.cfm. All but 2 of the recommendations were supported unanimously.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Panelists' Recommendations Based on Available Evidence

Rating

A: Strongly recommends. The recommendation is based on good evidence that the service or intervention can improve important health outcomes.

B: Recommends. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes.

C: Recommends. The recommendation is based on expert opinion.

D: Recommends against. The recommendation is based on expert opinion.

E: Recommends against. The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.

F: Strongly recommends against. The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.

I: Recommends neither for nor against. The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention because evidence is lacking that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. As a result, the balance of benefits and harms cannot be determined.

Source: Adapted from the US Preventive Services Task Force, Agency for Healthcare Research and Quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Subclinical Thyroid Disease: Questions and Recommendations

Subclinical thyroid disease is, by its very nature, a laboratory diagnosis. Patients with subclinical disease have few or no definitive clinical signs or symptoms of thyroid dysfunction. Thus, it is critically important that the normal reference range for thyroid stimulating hormone (TSH) be standardized and that laboratories engage in appropriate quality control procedures to ensure that the results they report are accurate and reproducible. The TSH method used should have a functional sensitivity of at least 0.02 mIU/L, and the functional sensitivity should be independently established by each laboratory.

What Is the Definition of Subclinical Hypothyroidism?
Subclinical hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum free T_4 (FT_4) concentration is within its reference range. Other causes of an elevated serum TSH must be excluded, for example: recent adjustments in levothyroxine dosage with failure to reach a steady state, particularly in poorly compliant patients; transient increase in serum TSH in hospitalized patients during recovery from severe illness or during recovery from destructive thyroiditis, including post-viral subacute thyroiditis and postpartum thyroiditis; untreated primary adrenal insufficiency; patients receiving recombinant human TSH injections; and the presence of heterophilic antibodies against mouse proteins, which cause falsely high TSH concentrations in some assays. Although central hypothyroidism (usually hypothalamic) may cause a mildly elevated serum TSH concentration (due to a circulating bioinactive TSH molecule), the serum FT_4 concentration is generally clearly low in these patients.

Some investigators suggest that the upper limit of normal for serum TSH concentration should be 2.5 mIU/L in a population rigorously screened to exclude thyroid disease or drugs that influence thyroid function. In support of this position are a higher rate of progression to overt hypothyroidism and a higher prevalence of antithyroid antibodies in individuals with serum TSH higher than 2.5 mIU/L compared with those with serum TSH between 0.5 and 2.5 mIU/L. Although a serum TSH concentration higher than 2.5 but less than 4.5 mIU/L may identify some individuals with the earliest stage of hypothyroidism and those suspect for Hashimoto thyroiditis, there is no evidence for associated adverse consequences. Furthermore, serum TSH concentrations between 2.5 and 4.5 mIU/L may be due to minor technical problems in the TSH assay, circulating abnormal TSH isoforms, or heterophilic antibodies; normal individuals with serum TSH concentrations in this range would be misidentified as having hypothyroidism. Given these concerns as well as the pulsatile nature and continuous distribution of serum TSH

concentrations, the panel defined the reference range of normal serum TSH concentration as 0.45 to 4.5 mIU/L.

What Is the Definition of Subclinical Hyperthyroidism?

Subclinical hyperthyroidism is defined as a serum TSH concentration below the statistically defined lower limit of the reference range when serum FT_4 and T_3 concentrations are within their reference ranges. Other causes of a low serum TSH must be excluded. Subclinical hyperthyroidism may result from endogenous overproduction of thyroid hormone or intended or inadvertent overadministration of thyroid hormone. Among other causes of a low serum TSH concentration with normal concentrations of FT_4 are delayed recovery of the pituitary TSH-producing cells during or after therapy for hyperthyroidism, normal pregnancy, various nonthyroidal illnesses (euthyroid sick syndrome), or the administration of dopamine, glucocorticoids, and possibly dobutamine. Although subnormal serum TSH concentrations are common in a variety of severe nonthyroidal illnesses, undetectable serum TSH concentrations (<0.01 mIU/L) are rare unless patients are receiving concomitant glucocorticoids (usually in high doses) or dopamine. Although patients with pituitary or hypothalamic failure (including anorexia nervosa) frequently have subnormal serum TSH concentrations, the FT_4 is also usually subnormal. When serum FT_4 is in the normal range, it is almost invariably in the lower part of the range in those with nonthyroidal illness in contrast to the high normal FT_4 concentration of typical subclinical hyperthyroidism.

Subclinical Hypothyroidism: Questions and Recommendations

What Are the Consequences of Untreated Subclinical Hypothyroidism?

Possible consequences of subclinical hypothyroidism include cardiac dysfunction or adverse cardiac end points (including atherosclerotic disease and cardiovascular mortality), elevation in total and low-density lipoprotein (LDL) cholesterol, systemic hypothyroid symptoms or neuropsychiatric symptoms, and progression to overt, symptomatic hypothyroidism (See Table 1 in the original document entitled "Quality of Evidence on the Strength of Association and Risks/Benefits of Treatment of Subclinical Hypothyroidism").

How Should Subclinical Hypothyroidism Be Evaluated?

If the serum TSH concentration is high and serum FT_4 concentration has not been measured, the TSH measurement should be repeated along with an FT_4 measurement at a minimum of 2 weeks, but no longer than 3 months, after the initial assessment. The panel recommends thyroid hormone therapy in individuals with elevated serum TSH concentrations whose FT_4 concentration is below the reference range (0.8-2.0 ng/dL [10.3-25.7 pmol/L]).

If a high serum TSH concentration is confirmed on repeat testing and serum FT_4 is within the reference range, the patient should be evaluated for signs and symptoms of hypothyroidism, previous treatment for hyperthyroidism (radioiodine, partial thyroidectomy), thyroid gland enlargement, or family history of thyroid disease. Lipid profiles should be reviewed. Women who are pregnant or hope to become pregnant in the near future deserve special consideration.

The evidence was insufficient to recommend either for or against routine measurement of anti-thyroid peroxidase (TPO) antibodies in patients with

subclinical hypothyroidism. The presence of anti-TPO antibodies identifies an autoimmune etiology for thyroid dysfunction and predicts a higher risk of developing overt hypothyroidism (4.3% per year vs. 2.6% per year in antibody-negative individuals). Still, antibody presence or absence does not change the diagnosis of subclinical hypothyroidism (which is based on serum TSH measurements) or the expected efficacy of treatment.

What Are the Risks and Benefits of Treating Subclinical Hypothyroidism? Among patients with untreated subclinical hypothyroidism, there is no single level of serum TSH at which clinical action is always either indicated or contraindicated. As the serum TSH concentration increases above 10 mIU/L, however, the basis for initiating treatment is more compelling. Clinical context is particularly important. This opinion reflects clinical experience and judgment as well as the literature that suggests improvement in symptoms and possible lowering of LDL cholesterol. There are no studies that demonstrate decreased morbidity or mortality with treatment. The potential risks of therapy are limited to the development of subclinical hyperthyroidism, which may occur in 14 to 21% of individuals treated with levothyroxine.

Subclinical Hypothyroidism With Serum TSH of 4.5 to 10 mIU/L. Although some studies suggest an association between subclinical hypothyroidism and systemic hypothyroid symptoms or cardiac dysfunction, others do not. No population-based studies examined symptoms in patients with serum TSH concentrations between 4.5 and 10 mIU/L. The likelihood of progression to overt hypothyroidism appears to be higher than for those with TSH levels lower than 4.5 mIU/L (see Table 1 in the original guideline document). Although early levothyroxine therapy does not alter the natural history of the disease, it may prevent symptoms and signs of overt disease in those who do progress. The available data do not confirm clear-cut benefits for early therapy compared with treatment when symptoms or overt hypothyroidism develop (see Table 1 of original document). Therefore, the panel does not recommend routine levothyroxine treatment for patients with TSH levels between 4.5 and 10 mIU/L, but thyroid function tests should be repeated at 6- to 12-month intervals to monitor for improvement or worsening in TSH level.

The panel realizes that some individuals with TSH levels between 4.5 and 10 mIU/L have symptoms compatible with hypothyroidism. Clinicians and patients may decide on a several-month trial of levothyroxine, while monitoring for improvement in hypothyroid-type symptoms. Continuation of therapy should be predicated on clear symptomatic benefit. Still, the panel considers the likelihood of improvement small, and it must be balanced against the inconvenience, expense, and potential risks of therapy. Physicians and patients must understand that there is insufficient evidence to expect therapeutic benefit in patients in this group and that distinguishing a true therapeutic effect from a placebo effect in an individual patient is difficult. Still, the possibility that some patients may benefit cannot be ruled out. Physicians and patients should understand the natural history of subclinical hypothyroidism and the small but definite risk of progression to overt hypothyroidism. The special case of pregnancy or the planned pregnancy in women with subclinical hypothyroidism is discussed below.

Subclinical Hypothyroidism With Serum TSH Higher Than 10 mIU/L. Levothyroxine therapy is reasonable for patients with subclinical hypothyroidism and serum TSH higher than 10 mIU/L. The rate of progression is 5% in comparison with patients

with lower levels of TSH, and treatment may potentially prevent the manifestations and consequences of hypothyroidism in those patients who do progress. Still, the evidence that therapy will reduce total and LDL cholesterol levels and improve symptoms in these patients is inconclusive (See Table 2 of original guideline document).

Subclinical Hypothyroidism During Pregnancy. The panel gave a rating of "fair" to the evidence of an association between subclinical hypothyroidism and adverse outcomes of pregnancy for either the fetus or the mother. However, the panel made the following recommendation: a TSH level might be obtained in pregnant women and women who wish to become pregnant if they have a family or personal history of thyroid disease, physical findings or symptoms suggestive of goiter or hypothyroidism, type 1 diabetes mellitus, or a personal history of autoimmune disorders. For women who already take levothyroxine but whose TSH level is in the subclinical hypothyroidism range, compliance and appropriateness of dose should be assessed.

Pregnant women or women of childbearing potential planning to become pregnant who are found to have elevated serum TSH should be treated with levothyroxine to restore the serum TSH concentration to the reference range. This recommendation is based on the possible association between high TSH and either increased fetal wastage or subsequent neuropsychological complications occurring in the offspring due to thyroid insufficiency. Although there are no published intervention trials assessing the benefits of thyroid hormone replacement in this special population, the potential benefit-risk ratio of levothyroxine therapy justifies its use. It is important to note that the requirement for levothyroxine in treated hypothyroid women frequently increases during pregnancy. Therefore, serum TSH concentration should be monitored every 6 to 8 weeks during pregnancy and the levothyroxine dose modified as needed. The risks of appropriately managed levothyroxine therapy in pregnancy are minimal. Continuation of levothyroxine treatment post partum is beyond the scope of this discussion.

Subclinical Hypothyroidism in Treated Overt Hypothyroid Individuals. When subclinical hypothyroidism is noted in levothyroxine-treated patients with overt hypothyroidism, the dosage of levothyroxine should be adjusted to bring the serum TSH into the reference range. Whether the target TSH level should be in the lower half of the reference range is controversial because there are no data demonstrating improved clinical outcomes with this strategy. Nevertheless, when the serum TSH is in the upper half of the reference range and levothyroxine-treated patients continue to note symptoms suggestive of hypothyroidism, it is reasonable to increase the levothyroxine dosage to bring the serum TSH into the lower portion of the reference range. The rapidity of the dosage adjustment depends on the patient's age and medical comorbidities. Minimal TSH elevations may not require dosage adjustment in patients who feel well, particularly those with arrhythmias or other cardiac disorders.

Subclinical Hyperthyroidism: Questions and Recommendations

What Are the Consequences of Untreated Subclinical Hyperthyroidism?

Assessment of Evidence. The panel evaluated the strength of the evidence for the association of untreated subclinical hyperthyroidism and the following clinical

outcomes: progression to overt hyperthyroidism, adverse cardiac end points, atrial fibrillation, cardiac dysfunction, systemic and neuropsychiatric symptoms, reduced bone mineral density and fractures (See Table 2 in the original guideline document). The panel also assessed the strength of the association between the TSH level and the risks and benefits of treatment (See Table 2 in the original guideline document). Similar to the approach taken in many reported studies, the panel classified patients with subclinical hyperthyroidism into 2 categories: those with mildly low but detectable serum TSH (0.1-0.45 mIU/L) and those with a clearly low serum TSH (<0.1 mIU/L). In all clinical settings, causes of subnormal serum TSH concentration other than subclinical hyperthyroidism must be excluded.

How Should Subclinical Hyperthyroidism Be Evaluated?

Individuals With Serum TSH 0.1 to 0.45 mIU/L Not Treated With Levothyroxine. If serum TSH is reported to be between 0.1 and 0.45 mIU/L, the measurement should be repeated for confirmation. The panel recommends measuring FT_4 and either total T_3 or FT_3 levels to exclude central hypothyroidism or nonthyroidal illness. Clinical circumstances dictate when the retesting should occur. For patients with atrial fibrillation, cardiac disease, or other serious medical conditions, repeat testing within 2 weeks is prudent. When these factors are absent, repeat testing is recommended within 3 months.

If the repeat serum TSH concentration remains higher than 0.1 but lower than 0.45 mIU/L, with normal FT_4 and T_3 concentrations, and the patient has no signs or symptoms of cardiac disease, atrial fibrillation, or other arrhythmias, retesting should occur at 3- to 12-month intervals, until either serum TSH normalizes or the clinician and patient are confident that the condition is stable. Patients with known nodular thyroid disease may develop overt hyperthyroidism when exposed to excess iodine (e.g., radiographic contrast agents) and require special consideration.

Individuals With a Serum TSH Lower Than 0.1 mIU/L. If serum TSH concentration is lower than 0.1 mIU/L, the panel recommends repeating the measurement, along with an FT_4 and a total T_3 or FT_3, within 4 weeks of the initial measurement. If the patient has signs or symptoms of cardiac disease, atrial fibrillation, or other arrhythmia, or medical issues requiring urgent diagnosis and treatment, these tests should be performed within a shorter interval particularly if there are signs or symptoms of hyperthyroidism.

Endogenous Subclinical Hyperthyroidism (TSH Lower Than 0.45 mIU/L). The panel recommends further evaluation to establish the etiology of the low serum TSH. A radioactive iodine uptake measurement and scan can distinguish between destructive thyroiditis and hyperthyroidism due to Graves' disease or nodular goiter.

What Are the Risks and Benefits of Treatment of Subclinical Hyperthyroidism?

The risks of treatment of subclinical hyperthyroidism with antithyroid drugs are potential allergic reactions including agranulocytosis. Radioactive iodine therapy commonly causes hypothyroidism and may cause exacerbation of hyperthyroidism or Graves eye disease.

Exogenous Subclinical Hyperthyroidism With TSH 0.1 to 0.45 mIU/L. When the serum TSH concentration is between 0.1 and 0.45 mIU/L in a levothyroxine-treated individual, the indication for thyroid hormone therapy should be reviewed. Many patients with thyroid cancer and some patients with thyroid nodules require TSH suppression, and the target TSH level should be reviewed by the treating endocrinologist or other physician. When levothyroxine is prescribed for hypothyroidism in the absence of thyroid nodules or thyroid cancer, the panel recommends decreasing the dosage of levothyroxine to allow serum TSH to increase toward the reference range. This dosage adjustment may be particularly important when the serum TSH is in the lower part of the range (See Table 2 in the original guideline document).

Exogenous Subclinical Hyperthyroidism With TSH Lower Than 0.1 mIU/L. When the serum TSH concentration is lower than 0.1 mIU/L in a levothyroxine-treated individual, the indication for thyroid hormone therapy should be reviewed. For patients with thyroid cancer and thyroid nodules, the target serum TSH value should be reviewed by the patient's endocrinologist or treating physician. When levothyroxine is prescribed for hypothyroidism in the absence of thyroid nodules or thyroid cancer, the panel recommends decreasing the dosage of levothyroxine to allow serum TSH to increase toward the reference range.

Endogenous Subclinical Hyperthyroidism (Serum TSH 0.1-0.45 mIU/L). The panel recommends against routine treatment for all patients whose TSH is mildly decreased (0.1-0.45 mIU/L). The panel found insufficient evidence to establish a clear association between this mild degree of hyperthyroidism and adverse clinical outcomes, including atrial fibrillation. However, because of a possible association with increased cardiovascular mortality, clinicians might consider treatment of elderly individuals, despite the absence of supportive data from intervention trials.

Endogenous Subclinical Hyperthyroidism (Serum TSH Lower Than 0.1 mIU/L). Subclinical hyperthyroidism due to destructive thyroiditis (including post-viral subacute thyroiditis and postpartum thyroiditis) resolves spontaneously. Treatment, apart from symptomatic therapy (e.g., beta-blockers), is usually not required.

The panel recommends that treatment be considered for subclinical hyperthyroidism (TSH <0.1 mIU/L) due to Graves' or nodular thyroid disease. The panel recognizes the paucity of intervention trials, apart from those demonstrating stabilization of bone density. However, the panel was concerned about the risk of atrial fibrillation and/or bone loss, particularly in the elderly. Specifically, treatment should be considered for patients who are older than 60 years and for those with or at increased risk for heart disease, osteopenia, or osteoporosis (including estrogen-deficient women), or for those with symptoms suggestive of hyperthyroidism. Younger individuals with subclinical hyperthyroidism and serum TSH persistently (months) lower than 0.1 mIU/L may be offered therapy or follow-up depending on individual considerations.

Is Screening for Subclinical Thyroid Disease Warranted?

The rationale for population screening hinges on the high prevalence of subclinical thyroid dysfunction in the adult population and on the potential health benefits and risks of detecting and treating these diseases. The panel used the US Preventive Services Task Force criteria for recommending a screening test, which

requires evidence of effectiveness of early detection. One of the most important criteria for recommending a screening test is that screening asymptomatic persons and treating them for the condition should result in improved measurable and important health outcomes when compared with persons who are not screened and who present with signs or symptoms of the disease. An alternative to population screening is aggressive case finding, defined as the application of a test to a person presenting to a clinician for a reason usually unrelated to the test being applied to determine the person's likelihood of having a particular disease or condition.

Thyroid dysfunction is more prevalent in certain population groups, including women older than 60 years, persons with previous radiation treatment of the thyroid gland (radioactive iodine or therapeutic external beam radiation), those who have had previous thyroid surgery or thyroid dysfunction, and those who have type 1 diabetes mellitus, a personal history of autoimmune disease, a family history of thyroid disease, or atrial fibrillation. The panel recommends aggressive case finding in these high-risk groups. The panel also endorses thyroid function testing (serum TSH measurement) for patients seeking medical care who have signs or symptoms suggestive of thyroid dysfunction or those being evaluated for palpable thyroid abnormalities.

The panel recommends against population-based screening for thyroid disease. Case ascertainment in certain high-risk groups is encouraged. The panel finds the evidence insufficient to recommend for or against routine determination of TSH levels (screening) in pregnant women or women planning to become pregnant. It is reasonable to consider serum TSH measurement for women with a family history of thyroid disease, prior thyroid dysfunction, symptoms or physical findings suggestive of hypothyroidism or hyperthyroidism, an abnormal thyroid gland on examination, type 1 diabetes mellitus, or a personal history of an autoimmune disorder.

Conclusion

The review of the literature revealed a striking paucity of evidence bearing on the major clinical questions examined. These recommendations are based on the existing evidence and the panel members' clinical experience, but they are limited by the paucity of definitive data. Well-conceived and executed intervention trials are needed to bring definitive data to light on these questions. Until such data are available, clinical judgment and patients' preferences remain paramount. Although the panel recommended against population screening for subclinical thyroid disease, clinicians are encouraged to make individual patient assessments when determining the need for testing and treatment.

Definitions:

Strength of the Overall Evidence

Good

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair

Evidence is sufficient to determine effects on health outcomes, but the strength of

the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.

Insufficient
Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Source: Adapted from the US Preventive Services Task Force, Agency for Healthcare Research and Quality.

Strength of Panelists' Recommendations Based on Available Evidence

Rating

A: Strongly recommends. The recommendation is based on good evidence that the service or intervention can improve important health outcomes.

B: Recommends. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes.

C: Recommends. The recommendation is based on expert opinion.

D: Recommends against. The recommendation is based on expert opinion.

E: Recommends against. The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.

F: Strongly recommends against. The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.

I: Recommends neither for nor against. The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention because evidence is lacking that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. As a result, the balance of benefits and harms cannot be determined.

Source: Adapted from the US Preventive Services Task Force, Agency for Healthcare Research and Quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on the existing evidence and the panels' clinical experience, but they are limited by the paucity of definitive data.

The panel examined the quality of the evidence for the strength of an association with certain adverse consequences of subclinical hypothyroid disease and the quality of the evidence addressing the risks and benefits of treatment (See Table 1 of the original guideline document.)

The panel evaluated the strength of the evidence for the association of untreated subclinical hyperthyroidism and the following clinical outcomes: progression to overt hyperthyroidism, adverse cardiac end points, atrial fibrillation, cardiac dysfunction, systemic and neuropsychiatric symptoms, reduced bone mineral density, and fractures). The panel also assessed the strength of the association between the thyroid-stimulating hormone (TSH) level and the risks and benefits of treatment (See Table 2 of the original guideline document.)

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate evaluation and treatment of subclinical hypothyroidism and hyperthyroidism
- Avoidance of the risks of adverse events associated with the treatment of patients with subclinical thyroid disease
- Positive outcomes of treatment are associated in individuals at high risk of thyroid dysfunction, including pregnant women and women over 60 years of age.

POTENTIAL HARMS

- Possible consequences of untreated subclinical hypothyroidism include cardiac dysfunction or adverse cardiac end points (including atherosclerotic disease and cardiovascular mortality), elevation in total and low-density lipoprotein (LDL) cholesterol, systemic hypothyroid symptoms or neuropsychiatric symptoms and progression to overt, symptomatic hypothyroidism.
- Possible consequences of untreated subclinical hyperthyroidism include progression to overt hyperthyroidism, adverse cardiac end points, atrial fibrillation, cardiac dysfunction and reduced bone mineral density.
- The potential risks of therapy in subclinical hypothyroidism are limited to the development of subclinical hyperthyroidism, which may occur in 14 to 21% of individuals treated with levothyroxine.
- The risks of treatment of subclinical hyperthyroidism with antithyroid drugs are potential allergic reactions including agranulocytosis. Radioactive iodine therapy commonly causes hypothyroidism and may cause exacerbation of hyperthyroidism or Graves' eye disease.

QUALIFYING STATEMENTS

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Statements made in this publication do not represent the official policy or endorsement of Agency for Healthcare Research and Quality (AHRQ) or the federal government. Neither do statements made in this article reflect official policy of the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society organizers of the consensus development conference.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004 Jan 14;291(2):228-38. [96 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jan 14

GUIDELINE DEVELOPER(S)

Consensus Conference Panel on Subclinical Thyroid Disease - Independent Expert Panel

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GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Burman has served on the speaker's bureau for Abbott Laboratories, as a consultant for New River Pharmaceuticals, and as an advisor to Norovax Inc.

The sponsors had no role in planning the meeting, selection of participants, data collection or analysis, or manuscript preparation. None of the authors had a financial relationship with the sponsors. Some did give lectures and received honoraria that were occasionally provided by unrestricted educational grants from the sponsors.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available to subscribers only of The Journal of the American Medical Association.

Print copies: Available from the Society Services, The Endocrine Society, 8401 Connecticut Ave, Suite 900, Chevy Chase, MD 20815 (e-mail: societyservices@endo-society.org).

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on November 11, 2004.

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